said [a] second probe capable of specifically hybridizing to a part of the BCR gene on the other side of said chromosomal aberration, wherein said probes hybridize to an aberrant chromosome[a hybridization site for the first probe and a hybridization site for the second probe are brought within approximately 800 kb of each other by said chromosomal aberration].

Please add the following new claim:

--35. The composition of claim 1 wherein the aberrant chromosome is the Philadelphia chromosome.--

REMARKS

I. Status of the Claims

Claims 1-3, 5, 11, 21-30 and 32-34 have been amended. Claim 35 has been added. Claims 1-3 and 5-35 are presently in the case and are presented for reconsideration. A copy of the pending claims is attached hereto as Exhibit A.

The Action properly found that claims 3, 4, 16 and 24-28 "are allowable over the art as the art does not teach or fairly suggest providing dual labeled probes or primers, or the specific probes recited in the claims. The claims would be allowable subject to overcoming 112 second rejections above and if rewritten as independent claims." Office Action mailed 12/12/97, pp. 8-9.

Independent claims 1 and 2 have been amended to recite "at least two nucleic acid probes, each labeled with a distinguishable label." Claims 1 and 2 have been further amended to clarify that the claimed composition comprises at least two probes and may comprise more than two probes.

As stated on pg. 13, lines 20-22 of the Specification, a combination of, for example, three probes may be used to detect both the p190 and p210 molecular subtypes of the bcr:abl fusion.

Claims 1 and 2 have also been amended to further clarify the subject matter of the invention by substituting the word "distinguishable" for "distinct" to describe the probe labels. Support for such language is found in the Specification at least at pg. 10, line 20 and in pending claim 6. As noted in the Office Action, "there was no motivation in the art at the time of filing to label the PCR probes of Kawasaki with two distinguishable labels or to provide hybridization probes with two distinguishable labels." Office Action mailed 12/12/97 at pg. 10, lines 4-6.

Claim 1 has been amended to recite a chromosomal aberration "having an ABL gene side and a BCR gene side." It was well known in the art that the ABL and BCR genes are located on opposite sides of the chromosomal translocation resulting in the Philadelphia chromosome. Support for this amendment is found in the Specification at least in FIG. 2A and 2B and at pg. 20, lines 1-28.

New claim 35 has been added, reciting the composition of claim 1 wherein the aberrant chromosome is the Philadelphia chromosome. Support for this claim is found throughout the Specification, with specific examples at pg. 2, line 37 through pg. 3, line 12; pg. 11, line 30 through pg. 12, line 19; pg. 13, line 4 through pg. 14, line 25; and Examples 1 and 2. Claim 2 has been amended to track the language of previous claim 1, and claim 3 has been amended to track the language of previous claim 4.

Applicant notes that the rejection of claims 1-22, 29 and 31-33 under 35 U.S.C. § 112, first paragraph, as lacking an enabling disclosure has been withdrawn. Office Action mailed 12/12/97 at

page 9. The remaining specific grounds for rejection and Applicant's response thereto are set out in detail below.

II. Rejection of Claims 1-3, 5-34 Under 35 U.S.C. § 112, Second Paragraph.

The Examiner has rejected claims 1-3 and 5-34 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner raises a number of distinct points in finding a lack of enablement. Each of these concerns is addressed below.

Claim 1 - is rejected as indefinite in the recitation of "a hybridization site" as being unclear if the claim could encompass hybridization sites within RNA transcripts resulting from the translocation. Claims 1 and 2 have been amended to recite "wherein said probes hybridize to an aberrant chromosome." The claim as amended clarifies that the hybridization sites within the scope of the invention are part of chromosomal DNA and not RNA transcripts. Similar language has been incorporated into independent claim 34. Support for these amendments may be found in the Specification at least at pg. 12, lines 31-32.

Claim 5 - has been amended to depend from claim 1. Claims 5-7 are therefore no longer dependent from a canceled claim.

Claims 21-23 - are rejected as indefinite in the recitation of "as illustrated in." This recitation has been removed from the amended claims. The Action notes that the meaning of the "first exon of

the BCR gene" and the "last exon of the ABL gene" would be understood to those of ordinary skill in the art. Office Action mailed 12/12/97 at page 3. Claim 21 has been amended to remove the recitation of the "5' region" of the major breakpoint cluster. The Action acknowledges that those of skill in the art would understand that the major breakpoint cluster region is defined by a specific type of DNA sequence rearrangement. Office Action mailed 12/12/97 at page 3.

Claim 29 - has been amended to remove the recitation to the "control probe."

Claims 32 and 33 - have been amended to more clearly point out and distinctly claim the subject matter which Applicant regards as the invention. Claim 32 has been amended to clarify that the presence of the fusion gene is diagnostic or prognostic for ALL, while claim 33 has been amended to clarify that the presence of the fusion gene is diagnostic or prognostic for CML.

III. Rejection of Claims 1, 2, 8-10, 12-15, 17-22, 29-32 and 34 Under 35 U.S.C. § 102

The Action has rejected claims 1, 2, 8-10, 12-15, 17-22, 29-32 and 34 under 35 U.S.C. § 102(e) as being anticipated by Kawasaki *et al.* (U.S. Patent No. 5,057,410, filed Aug. 5, 1988). The Action states that Kawasaki *et al.* "teaches a method for the detection of RNA such as resulting from chromosomal translocations, including bcr-abl translocations, using the polymerase chain reaction. Compositions including two oligonucleotide primers are taught;...complementary with sequences of cDNA that are on the 3' side...and...the 5' side of the exon-exon junction." Action at pg. 4, last paragraph. Further, "The probes/primers taught by Kawasaki are diagnostic of ALL and CML (column 4, li[n]es 6-70)." Action at pg. 6.

Applicant respectfully submits that Kawasaki *et al.* does not anticipate the claims of the instant invention. Rejection under 35 U.S.C. § 102 is improper unless each and every element of the claimed invention is present in a single prior art reference. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986). Applicant submits that the instant invention incorporates several elements that are missing from the reference by Kawasaki *et al.*

The Action found claims 3, 4, 16 and 24-28 to be allowable over the art, as the art does not teach or fairly suggest providing distinguishable, dual labeled probes or primers, or the specific probes recited in the claims. Office Action mailed 12/12/97 at page 8. Independent claims 1 and 2 have been amended to recite the distinguishable, dual labeled probes previously found by the Action to be allowable in claim 3. Thus, independent claims 1 and 2 and dependent claims 3, 5-23 and 27-33 should be found allowable over the art, as they incorporate the recitations previously found to be allowable in claim 3. Similarly, amended claim 34 also recites the distinguishably labeled probes found by the Office Action to be allowable.

Further, independent claims 1, 2 and 34 and the corresponding dependent claims have been amended to clarify that the probes of the instant invention hybridize to an aberrant chromosome. The recitations of Kawasaki *et al.* are limited to chimeric mRNAs or the corresponding cDNAs. There is no mention in Kawasaki *et al.* and no motivation offered to design probes and primers for hybridization to chromosomal DNA. In fact, their procedure starts with isolation of mRNA, for example by guanidinium isothiocyanate extraction and RNA precipitation (Kawasaki *et al.*, col. 12, lines 54-61). In such a procedure, mRNA is separated from chromosomal DNA. Thus, in the method of Kawasaki *et al.* there would be no possibility of chromosomal hybridization to their probes or primers.

For similar reasons, claims 8-10 and 12-20 which recite probe hybridization to chromosomal DNA *in situ* in cells are also not anticipated by Kawasaki *et al.* Not only does Kawasaki *et al.* start by removing chromosomal DNA from their sample, but the PCR procedure utilized by Kawasaki *et al.* is not suited to the use of *in situ* hybridization and detection as taught in the instant application. In PCR amplification, the amplified oligonucleotides are thermally detached from their templates following each amplification cycle.

Thus, if PCR were applied *in situ* to chromosomal DNA, the amplified product would be separated from the hybridization site after each cycle and lost to detection or, even worse, would provide non-specific background against which it would be impossible to detect a labeled chromosome. In sharp contrast, in the instant invention the distinguishable labeled probes are designed to be detected while still bound to their chromosomal hybridization sites. This element is not taught, nor is any motivation offered to derive such an invention, by Kawasaki *et al.*

Not only does Kawasaki *et al.* not disclose the instant invention, it actually "teaches away" from the central aspect of the invention. It is impermissible under the law to overlook aspects of the art that teach away from the claimed invention. Consideration must be given to prior art that would lead one away from the invention as well as that which is argued to lead toward it. *Mendenhall v. Astec Industries, Inc.*, 13 USPQ2d 1913, 1939 (Tenn. 1988), *aff'd*, 13 USPQ 2d 1956 (Fed. Cir. 1989).

The skilled practitioner of the art, reading Kawasaki, would conclude that the way to detect a bcr:abl translocation is by PCR amplification of the mRNA transcript, not by direct detection of the rearranged chromosome. Although the instant application is addressed towards compositions and kits for use in detecting such rearranged chromosomes, rather than methods of detection, an

essential feature of the claimed compositions is that they are designed to function in the intended use - that of detecting aberrant chromosomes.

According to MPEP § 2111.03, "Intended use recitations...cannot be entirely disregarded. However, in...composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim." Applicant submits that the instant application presents the situation where the compositions of Kawasaki are not capable of performing the intended use.

As the Specification makes clear, the size of the probes used in such compositions is of significance. This is because, "when a short sequence hybridizes, the signal may be too weak to be detected." Specification at pg. 9, lines 24-25. Thus, "this invention takes advantage of probes large enough to give an intense signal yet specifically targeted to a genomic sequence." Specification at pg. 10, lines 17-19.

Kawasaki *et al.* recites primers that "typically" contain 15-25 nucleotides. In contrast, the probes contained in the Examples of the instant application are respectively 18 kb, 35 kb and 18 kb long. There is no showing in the art or of record that a 25 base oligonucleotide is capable of performing the specific chromosomal hybridization and labeling described in the instant application, using probes that are thousands of basepairs long.

An essential property of Kawasaki's probes and primers, hybridization to messenger RNA or the corresponding cDNA, makes them particularly unsuited for use in detecting rearranged chromosomes. Consider the *in situ* use of a fluorescent probe that can bind to either mRNA or chromosomal DNA. The ratios of mRNA to corresponding DNA sequences in the cell are

hundreds or even thousands to one. One would end up with a cell with hundreds of randomly distributed, fluorescently labeled mRNA molecules, compared to, at most, two labeled DNA molecules. Fluorescent detection of the labeled DNA against this background would be virtually impossible.

Applicant respectfully asserts that the probes and primers of Kawasaki *et al.* are not equivalent to the chromosome labeling probes of the instant invention. Any "inherent" capability of the probes of Kawasaki *et al.* to hybridize (at least to some extent) with chromosomal DNA *in situ* in cells (Action at page 7) is insufficient to anticipate the pending claims. The Federal Circuit recently remanded a case to the Board due to insufficient reasons supporting an attempted anticipation rejection, stressing that "necessary findings must be expressed with sufficient particularity". *Gechter v. Davidson*, 43 USPQ 2d 1030 (Fed. Cir. 1997).

Further, "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d, 1461, 1464 (Bd. Pat. App. & Inter. 1990), also MPEP § 2112. In the case at hand, there has been no provision of objective evidence or cogent technical reasoning to support the conclusion of inherency as to the ability of the probes and primers of Kawasaki *et al.* to label genomic chromosomal DNA, using the dual label FISH technique of the instant application. There is no evidence of record that the probes of Kawasaki *et al.* are inherently capable of performing the function for which the compositions of the instant application were designed, the specific labeling of genomic DNA sequences.

For the reasons cited above, Applicant submits that the instant invention does not "read on" Kawasaki *et al.* and rejection of the claims under 35 U.S.C. § 102 is improper. Reconsideration and withdrawal of the rejection is respectfully requested.

IV. Rejection of Claims 1, 2, 8-12, 14, 17-20, 22, 23, 29, 31 and 34 Under 35 U.S.C. § 103

The Action has rejected claims 1, 2, 8-12, 14, 17-20, 22, 23, 29, 31 and 34 under 35 U.S.C. § 103 as being unpatentable over Stephenson *et al.* (U.S. Patent No. 4,681,840, 1987). Applicant respectfully submits that Stephenson *et al.* does not make obvious the pending claims of the instant invention.

The Action acknowledges that "Stephenson does not envision the use of dual labeled probes to detect bcr-abl in a single assay;" and that "the art does not teach or fairly suggest providing dual labeled probes or primers, or the specific probes recited in the claims." Office Action mailed 12/12/97 at page 8. Further, "there was not motivation in the art at the time of filing to...provide hybridization probes with two distinguishable labels." Office Action mailed 12/12/97 at pg. 10, lines 4-6. As discussed above, independent claims 1, 2 and 34, along with dependent claims 5-23 and 27-33 have been amended to incorporate the recitations of claim 3 to distinguishably labeled probes.

As claim 3 has already been found to be allowable over the art, the pending claims as amended should also be found allowable over the art. According to 35 U.S.C. § 112, fourth paragraph, it is well settled patent law that a dependent claim necessarily incorporates the limitations of the claim or claims upon which it depends. "A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers." *Twin Disc*

Inc., v. U.S., 231 USPQ 417 (Cl. Ct. 1986). Thus, independent claims 1, 2 and 34, as well as dependent claims 3, 5-23 and 27-33, all recite the unique feature of two or more distinguishable labeled probes designed to detect a chromosomal aberration. This feature has already been found sufficient to distinguish the instant invention from the prior art under both §102 and §103.

It is important to remember what is necessary to render each of the present claims legally obvious. In *In re O'Farrell*, 7 USPQ 2d 1673 (Fed. Cir. 1988), it was held that, in order for a reference or references to render unpatentable an invention, it must be shown that the reference or references contain:

(1) detailed enabling methodology for practicing the claimed invention;

(2) a suggestion for modifying the prior art to practice the claimed invention; and

(3) evidence suggesting that the invention would be successful.

There is nothing in the cited references that even comes close to providing a detailed enabling methodology for practicing the claimed invention. Kawasaki *et al.* recites very short oligonucleotide primers, designed to bind to mRNA, while Stephenson *et al.* recites a single nucleic acid probe molecule containing at least three distinct nucleotide sequences from the bcr:abl translocation site. Neither Kawasaki nor Stephenson, alone or in combination, fairly suggest the instant invention, designing two or more distinguishable labeled probes of sufficient size and complexity to specifically bind to chromosomal hybridization sites flanking the translocation site of bcr:abl. In fact, both references teach away from the instant invention - Kawasaki *et al.* by suggesting bcr:abl detection targeted to mRNA and Stephenson *et al.* by suggesting the use of a single genomic probe to detect a recombinant bcr:abl. Neither reference suggests targeting two distinguishable labeled genomic probes to regions flanking the bcr:abl translocation site. The cited

art even more clearly lack evidence suggesting that the instant invention as claimed would be successful.

Applicant further submits that a combination of Stephenson *et al.* with Kawasaki *et al.* could not properly be applied in the instant case. In combining references, something in the prior art as a whole must suggest the desirability, and thus the obviousness, of making the combination. *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 USPQ 2d 1434 (Fed. Cir. 1988). Legal obviousness is not established by citing references that "skirt all around but do not as a whole suggest the claimed invention". *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986).

The patentability of "combinations" is of an ancient authority. In considering obviousness, the Federal Circuit stated: "Virtually all inventions are 'combinations', and *every* invention is formed of 'old elements'....Only God works from nothing. Man must work with old elements". *Wright*, 6 USPQ 2d at 1962.

In the case of *In re Vaeck*, 20 USPQ 2d 1438 (Fed. Cir. 1991), the Federal Circuit took the *O'Farrell* doctrine a step further. In *Vaeck* the Federal Circuit stated that in order for an Examiner to make out a *prima facie* case of obviousness two things must be shown:

(1) that the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition; and

(2) that the prior art must demonstrate a reasonable expectation of success of the invention.

The court in *Vaeck* went on to emphasize that both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. Here, the reference of Stephenson *et al.* discloses only a single genomic probe, targeted to the translocation

site of bcr:abl. There is no mention of dual labeled probes targeted to regions of the chromosome located on either side of the translocation site. There is, therefore, no suggestion of the invention in the cited art and the first requirement of *In re Vaeck* is not met.

Even if there were "some suggestion" to motivate one towards the claimed invention in the cited art, which is rigorously contested, this would still not render the present claims legally obvious. As the PTO's reviewing court has emphasized, it is not appropriate for the PTO to inquire, pursuant to §103, as to "what was 'obvious to try' [in]...explor[ing]a...general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell* at 1681. "Obvious to try" is not legally obvious under 35 U.S.C. § 103.

The *Vaeck* decision stresses the need for a reasonable expectation of success to be present in the prior art. In *Vaeck*, the expression of *Bacillus* insecticidal toxins in cyanobacteria was found not to be legally obvious in light of a combination of prior art which disclosed (a) the expression of a reporter gene (CAT) in cyanobacteria, and (b) the expression of *Bacillus* toxins in other bacterial hosts, including *B. megaterium*, *B. subtilis*, and *E. coli*. The prior art references were held not to present evidence of a "reasonable expectation of success" for the expression of *Bacillus* insecticidal proteins in cyanobacteria.

The same lack of "reasonable expectation" is also true in the present case. The prior art references entirely fail to suggest that one could reasonably expect to detect a bcr:abl translocation by targeting distinguishable labeled genomic probes to hybridization sites located on either side of the translocation site. It is therefore clear that no reasonable expectation of success exists in the

cited art and the second requirement of *In re Vaeck* is not met. A proper *prima facie* case of legal obviousness has therefore not been made.

In light of the reasons recited above, Applicant submits that rejection under 35 U.S.C. § 103 was improperly applied against the original claims. None of the cited art, either alone or in combination, taught or suggested the claimed invention. The present claims even more clearly point out the differences between the invention and the prior art and are thus even further removed from the art. Accordingly, reconsideration and withdrawal of the § 103 rejection is respectfully requested

VII. Summary and Conclusion

In light of the foregoing comments, Applicant submits that all pending claims are in condition for allowance and solicits an early indication to that effect. Should Examiner Arthur feel that further discussion of any of the issues is merited, she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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Dated: June 11, 1998

EXHIBIT A: Pending Claims in Application Serial No. 07/784,222

The claims are listed below as they would appear if the requested amendments are entered in the case.

1. (Three times amended) A composition comprising at least two probes, each labeled with a distinguishable label, for detecting a chromosomal aberration involving the BCR and ABL genes, said chromosomal aberration having an ABL gene side and a BCR gene side, wherein one of said probes hybridizes to the ABL gene side of said chromosomal aberration and the other of said probes hybridizes to the BCR gene side of said chromosomal aberration, wherein said probes hybridize to an aberrant chromosome.

2. (Amended) A composition comprising at least two probes for detecting a chromosomal aberration, each probe labeled with a distinguishable label, wherein one of said probes hybridizes to a part of the ABL gene on one side of said chromosomal aberration and the other of said probes hybridizes to a part of the BCR gene on the other side of said chromosomal aberration, wherein said probes hybridize to an aberrant chromosome.

3. (Amended) The composition of claim 2 wherein said probes hybridize within approximately 800 kb of each other in said aberrant chromosome.

5. (Twice Amended) The composition of claim 1 wherein the labels comprise fluorescent labels.

6. (Amended) The composition of claim 5 wherein the fluorescent labels are distinguishable under a microscope as different colors.

7. (Amended) The composition of claim 6 wherein the fluorescent labels comprise digoxigenin-11-dUTP and biotin-11-dUTP.

8. (Amended) The composition of claim 1 wherein the probes hybridize with chromosomal DNA *in situ* in cells.

9. (Amended) The composition of claim 8 wherein the cells comprise those in interphase of mitotic division.

10. (Amended) The composition of claim 9 wherein the probes after hybridization are juxtaposed as doublets if a chromosomal aberration is present.

11. (Three Times Amended) The composition of claim 1 wherein one of said probes is capable of hybridizing to at least a portion of the last exon of the ABL gene and the other of said probes is capable of hybridizing to at least a portion of exon I of the BCR gene.

12. (Twice Amended) The composition of claim 10 wherein the chromosomal aberration is further defined as comprising a translocation, said translocation formed by breakpoints which occur on the long arms of human chromosomes 9 and 22.

13. (Amended) The composition of claim 12 wherein the translocation breakpoints are further defined as occurring at the locations designated t(9;22) (q11;q34).

14. (Amended) The composition of claim 13 wherein the translocation breakpoints are further defined to occur in the BCR and ABL genes respectively, and a fusion gene is formed by the translocation, and said fusion gene comprises portions of the BCR and ABL genes.

15. (Twice Amended) The composition of claim 14 wherein the fusion gene encodes a protein p190.

16. (Twice Amended) The composition of claim 10 wherein the probes consist of those selected from probes PEM12, c-H-abl and MSB-1.

17. (Amended) The composition of claim 8 wherein the cells comprise a sample of human tissue.

18. (Amended) The composition of claim 17 wherein the human tissue sample comprises peripheral blood.

19. (Amended) The composition of claim 17 wherein the human tissue sample comprises bone marrow.

20. (Amended) The composition of claim 8 wherein the cells comprise a sample of cultured cells.

21. (Amended) The composition of claim 1 wherein one of said probes is capable of hybridizing to the major breakpoint cluster region (M-bcr) of chromosome 22.

22. (Twice Amended) The composition of claim 1 wherein one of said probes is capable of hybridizing to the first exon of the BCR gene.

23. (Twice Amended) The composition of claim 1 wherein one of said probes is capable of hybridizing to at least a part of the last exon of the ABL gene.

24. (Twice Amended) A genetic probe comprising PEM12.

25. (Twice Amended) A genetic probe comprising MSB-1.

26. (Twice Amended) A genetic probe comprising c-H-abl.

27. (Twice Amended) The composition of claim 1 wherein said probes comprise c-H-abl and MSB-1.

28. (Amended) The composition of claim 1 wherein said comprise c-H-abl and PEM12.

29. (Twice Amended) A kit for the detection of chromosomal aberrations comprising at least two genetic probes selected from claims 24, 25 and 26, each in separate containers.

30. (Amended) A kit for the detection of cancer in human cells, comprising:

a) a carrier being compartmentalized to hold multiple containers;

b) a first pair of containers including the pair of genetic probes of claims 24 and 26; and

c) a second pair of containers containing the pair of genetic probes of claims 25 and 26.

31. (Amended) The composition of claim 14 wherein the fusion gene encodes either of two proteins p190 and p210.

32. (Amended) The composition of claim 31 wherein the presence of said fusion gene is diagnostic or prognostic for acute lymphocytic leukemia (ALL).

33. (Amended) The composition of claim 31 wherein the presence of said fusion gene is diagnostic or prognostic for chronic myelogenous leukemia (CML).

34. (Amended) A kit for the detection of chromosomal aberrations, comprising a first and second nucleic acid probe, each labeled with a distinguishable label, said first probe capable of specifically hybridizing to a part of the ABL gene on one side of said chromosomal aberration and said second probe capable of specifically hybridizing to a part of the BCR gene on the other side of said chromosomal aberration, wherein said probes hybridize to an aberrant chromosome.

35. (New) The composition of claim 1 wherein the aberrant chromosome is the Philadelphia chromosome.